

## EDITORIAL COMMENT

## Lizard Spit and Reperfusion Injury\*

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Although the incidence of ST-segment elevation myocardial infarction (STEMI) is declining in industrialized nations, there are still an estimated 500,000 events annually in the U.S. (1). Furthermore, the in-hospital mortality is 6% to 7%, and over 15% of survivors to discharge experience a recurrent cardiovascular event by 6 months (2). Infarct size is the key determinant of outcome, and prompt reperfusion of the occluded epicardial artery is imperative to reduce infarction volume and improve mortality and morbidity. Paradoxically, however, reperfusion seems to contribute to additional myocardial damage over and above that caused by the original ischemic insult. This additional damage is known as reperfusion injury and if it could be prevented an already exemplary treatment would be further improved.

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The concept of reperfusion injury has been recognized and its existence debated for over 30 years (3). At the cellular level there are a variety of associated/causative pathophysiological processes, including oxidative stress, intracellular calcium dysregulation, inflammation, and rapid normalization of intracellular pH (4). Animal models suggest that reperfusion injury might contribute up to 50% of ultimate infarction volume (4), and therefore its prevention should improve outcome. Unfortunately, despite numerous interventions showing promise in preclinical studies, very few have proved effective in clinical trials, and none has yet impacted on routine clinical practice (4,5).

In this issue of the *Journal*, Timmers et al. (6) present data in which the incretin mimetic exenatide significantly reduces myocardial infarction and improves left ventricular (LV) contraction and relaxation when it is given at reperfusion. These findings gain clinical relevance and immedi-

acy through the use of an approved drug, a large animal model, and the assessment of infarction after a long duration of reperfusion.

Exenatide (sold commercially as “Byetta,” Amylin-Lilly, San Diego, California) is currently licensed for parenteral use as an adjunctive therapy in patients with poorly controlled type II diabetes. Exenatide is a synthetic analogue of exendin-4, also known as “lizard spit” and found in the salivary secretions of the Gila monster, *Heloderma suspectum* (7). This 39-residue reptilian peptide is pharmacologically similar to mammalian glucagon-like peptide (GLP)-1 with which it shares 53% of its primary amino acid sequence (7,8). The GLP-1 is a gut-derived incretin hormone that is secreted by the intestine in response to nutrients. Like GLP-1, exenatide’s glucoregulatory effects are mediated through a number of different mechanisms, including augmentation of glucose-stimulated insulin secretion (hence with low risk of a hypoglycemic overshoot), suppression of postprandial glucagon secretion, delayed gastric emptying, and hypothalamic-mediated satiety of appetite (9). These actions are thought to be mediated via the GLP-1 receptor present in the gastrointestinal tract, pancreas, lung, kidney, brain, and heart (10).

Importantly, exenatide lacks the alanine residue found at position 2 of GLP-1 that directs its degradation. Consequently, exenatide has a very much longer plasma half-life than GLP-1 (approximately 2.4 h vs. 1 to 4 min). The alanine-directed endopeptidase predominantly responsible for the breakdown of GLP-1 is dipeptidyl peptidase (DPP)-IV. Thus, orally available inhibitors of DPP-IV increase the half-life of GLP-1 and are licensed similarly to exenatide for the treatment of type II diabetes.

Exenatide/exendin-4 and GLP-1 are known to have a number of cardiovascular effects. In isolated perfused rat hearts exendin-4 reduced infarct size when administered at reperfusion (11). This effect was abrogated by co-administration of a GLP-1 receptor antagonist. However, the positive inotropic effect of exendin-4 was independent of the GLP-1 receptor (11). Such GLP-1 receptor-independent effects are expected, because exendin-4 is not a true reptilian homologue of GLP-1 (8).

Experiments in both isolated and in vivo rat hearts suggest that GLP-1 significantly attenuates reperfusion injury and reduces infarct size by approximately 50% when coadministered with a DPP-IV inhibitor (12). The GLP-1 seems equally protective when given before lethal ischemia as a preconditioning agent (13). In a model of sub-lethal ischemic injury, a 24-h intravenous infusion of GLP-1 after a 10-min circumflex coronary artery occlusion in the dog diminished stunning independent of alterations in systemic hemodynamic status and contractile function in the remote myocardium (14).

The GLP-1 also exerts important effects on the failing heart; a 48-h infusion of GLP-1 in a canine-model of pacing-induced cardiomyopathy resulted in enhanced myo-

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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cardial insulin sensitivity and contractility (15). More recently, chronic subcutaneous GLP-1 over 3 months in a rat model of hypertension-related heart failure improved myocardial glucose uptake and reduced myocyte apoptosis, contractile dysfunction, and group mortality from 66% to 28% (16).

These observations have begun to be translated into small, nonrandomized, pilot clinical studies. A 5-week continuous subcutaneous GLP-1 infusion in 12 patients with ejection fractions <40% and New York Heart Association functional class III to IV symptoms was associated with significant improvements in objective measures of LV function and symptoms in both diabetic and nondiabetic patients (17). A 48-h perioperative infusion of GLP-1 in patients with preserved LV function undergoing elective bypass surgery significantly reduced inotrope requirements and improved glycemic control in the immediate postoperative period (18). An open, nonrandomized, pilot study has even examined the role of GLP-1 in patients with STEMI reperfused by primary percutaneous coronary intervention. Eleven such patients with impaired LV systolic function (LVEF <40%) received a 72-h GLP-1 infusion starting on average 212 min after the onset of reperfusion (19). Despite this delay, the limited number of observations and an echocardiographic end point, GLP-1 significantly improved recovery of LVEF and regional/global wall motion compared with the 10 control subjects (19).

The data from Timmers et al. in this issue of the *Journal* (6) add further support to the cardioprotective effects of incretin analogues in a clinically applicable model of ischemia-reperfusion. The observed reduction in infarction (32.7% vs. 53.6%,  $p = 0.03$ ) with exenatide is impressive and accompanied by improvements in systolic and diastolic function as measured by echocardiography and invasive simultaneous measurement of LV pressure and volume. These end points were collected after 3 days of reperfusion, effectively excluding a false-positive finding resulting from the delay rather than the prevention of reperfusion injury, although it could be argued that the results are predictable on the basis of the findings with GLP-1 summarized in the preceding text. As already mentioned exenatide is not a true GLP-1 homologue (8). Furthermore, unlike GLP-1, its half-life allowed administration twice daily rather than by continuous infusion.

The authors are to be congratulated on a well-designed and highly translational study; however, mechanistic insight is still limited. Exenatide resulted in a significant increase in phosphorylated (active) Akt at 2 h, a reduction in proapoptotic caspase-3 at 4 h, and higher levels of antiapoptotic Bcl-2 and reduced oxidative stress at 72 h of reperfusion. However, it is not clear whether any of these effects are causally related to protection. Furthermore, it is not clear whether it is the exenatide itself and/or the consequent increase in serum insulin that initiate protection. In the end such nuances become less important when the model and the intervention are so clinically pertinent.

It is likely that we, as cardiologists, will become more familiar with exenatide and the DPP-IV inhibitors as the tsunami of type II diabetes washes over our practice. On the basis of the study of Timmers et al. (6), it is possible that we might have the beginning of a flood defense. There is appreciable circumstantial evidence that the incretins and their mimetics will reduce cardiovascular risk as well as improve outcomes in those with a cardiovascular event. However, in the competition to find interventions that reduce reperfusion injury in the clinic, there is only 1 measure that matters: hard clinical end points.

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**Key Words:** exenatide ■ glucagon-like peptide 1 ■ myocardial infarction ■ reperfusion.